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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/594,526

11/27/2006

Christophe D'Hulst

0512-1352

9478

466 7590 01/22/2009

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EXAMINER

PAGE, BRENT T

ART UNIT

PAPER NUMBER

1638

MAIL DATE

DELIVERY MODE

01/22/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.		Applicant(s)	
	10/594,526		D'HULST ET AL.	
	Examiner		Art Unit	
	BRENT PAGE		1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 November 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 10-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The Preliminary amendment filed on 09/28/2006 is hereby acknowledged. Claims 1-9 have been cancelled and claims 10-18 are pending and examined herein upon the merits.

Claim Rejections - 35 USC § 112-scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for random insertional mutagenesis and the screening of a phenotype wherein the enzymatic action of starch phosphorylase appears to be reduced or abolished, does not reasonably provide enablement for the insertion of any number of nucleotides at any point along any length of the starch phosphorylase gene wherein starch phosphorylase is switched off, nor does it provide enablement for any other method of switching off the starch phosphorylase gene in which starch grain size and/or starch content of any plant part is increased as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method for increasing the size of starch grains and/or starch content of a plant or plant part wherein a starch phosphorylase gene is switched off and the transformed plants, plant cell and seed therefrom. Claim 12 is drawn to the above method wherein the switching off is by inserting nucleotide(s) in a gene coding for said endogenous starch phosphorylase in a plant cell. It is noted that the claim does not actually specify the nucleotides are inserted into said gene because it does not contain the limit inserting nucleotide(s) ---in--- a gene coding... However, for examination purposes wherein it appears to be a typographical error, the claim is being interpreted to mean that the inserted nucleotides are in “a” starch phosphorylase coding gene.

In contrast, the specification only provides guidance for random insertional mutagenesis wherein a plant is isolated in which an endogenous starch phosphorylase gene has a tDNA insertion between exon6 and intron 6, designated as line DDS72, and does not provide guidance for any targeted insertion of nucleotides in a starch phosphorylase gene, or the insertion of tDNA in any other location in a starch phosphorylation, or guidance for any method other than insertional mutagenesis that would result in increased starch or increased starch grain size in plants or plant parts. The specification also does not provide guidance for switching off a starch phosphorylase that is not endogenous wherein the starch grains and/or content is increased.

Additionally, while the specification mentions UV irradiation (page 7, 2nd paragraph of instant specification), chemical mutagen (page 7 2nd paragraph of instant specification), transposon insertion (pages 7-8 of specification), RNAi

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interference (page 8 of the specification), antisense vectors (page 9 of specification), ribozymes (pages 8-9 of the specification), the “transwitch” method (page 9 of specification), and virus-induced gene silencing (page 9 of instant specification), for “switching off” starch phosphorylase, the state of the art does not indicate that these methods would affect starch accumulation. The specification does not provide guidance how each of these methods would work specifically with starch phosphorylase and only mentions these methods as generally known methods in the art. However, the specification indicates on page 1 and 2 that previous work with antisense repression on starch phosphorylase did not have a significant influence on the accumulation of starch (see the last paragraph on page 1 and the first 3 paragraphs of page 2). The specification does not provide any guidance specific for antisense repression that would contradict the state of the art, nor does the specification provide guidance for antisense expression constructs that differ from the prior art in a way that would lead to increase starch grain size and/or starch content.

Random insertional mutagenesis does not use the same mechanism as antisense repression, or RNAi interference and therefore on its own may not provide results that counter the state of the art regarding antisense repression as discussed above. The specification does not provide a working example of antisense or RNAi repression of starch phosphorylase, only the general method as mentioned above on page 8 and 9 of the specification wherein the specification states, regarding antisense repression, “Construction of the expression vectors used (for example carrying an antisense sequence of the

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endogenous starch phosphorylase gene) or of the iRNAs is within the capacity of a person skilled in the art using standard methods” (see page 9 3rd full paragraph). The specification also does not give guidance as to the mechanism by which the enzyme activity is repressed in the working example of the insertional mutant line DDS72, rendering other methods of gene silencing unpredictable in their affect on the phenotype of the plant. In other words, without knowing the mechanism by which the insertion silences the gene, it is unknown whether the gene is silenced at the transcriptional, translational, or enzymatic level. Since RNAi and antisense RNA, for example, work primarily at the transcript level, it is not known whether that method of silencing would be as effective as insertional mutagenesis. The prior art appears to suggest that it is not as effective based on the first 2 pages of the instant specification. Similarly, it is not known whether chemical mutagens, UV irradiation or viral-based methods, which function differently than insertional mutagenesis would be similarly effective and therefore would also be unpredictable in practice without detailed guidance.

Addressing the differences of antisense and RNAi approaches from insertional mutagenesis approaches in a review of insertional mutagenesis in plants, An et al (2005 Plant Cell Physiology 46:14-22) disclose “If an allele is not present, antisense or RNAi approaches to reducing gene expression are useful. However, these alternative methods may affect the expression of genes that are structurally similar to the target gene. In addition, a small amount of expression persists in antisense or RNAi plants, a level that is often sufficient to produce a

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normal phenotype" (see last paragraph on page 19). There is no guidance in the specification as to whether or not the transcript is present in the line with the tDNA insertion in starch phosphorylase, or even whether or not the protein is present, only that enzymatic function has been eliminated. Without knowing the mechanism in which this function has been eliminated it would be unpredictable what the effects of RNAi or antisense constructs would have on the starch phenotypes of the plants as broadly claimed.

Furthermore, insertional mutagenesis itself is unpredictable. In a review of tDNA insertional mutagenesis, An et al (2005 Plant Cell Physiology 46:14-22) disclose that "The phenotypic alterations observed in a T-DNA –tagged line are not necessarily due to the insertional mutation caused by the element. This is because T-DNA often inserts into more than one locus in a particular chromosome. Alternatively, other elements, such as endogenous transposons, might be involved in the mutant phenotype" (see last paragraph on page 19 for example). An et al also disclose "Therefore it is necessary to confirm those observations by analyzing additional lines that contain a mutation in the target gene" (see last paragraph on page 19, for example).

Given the state of the art, the disclosure by An et al, and the unpredictability as discussed above, it would be undue experimentation for one of skill in the art to evaluate all methods of switching off any starch phosphorylation gene and valuating the effects on the starch grains and starch composition as broadly claimed. Accordingly, Applicants are not enabled over the full scope of the claims.

Claim Rejections - 35 USC § 112-enablement

Claims 17-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for producing any plant with an altered size of starch grains and/or altered starch content comprising producing said plant with a SEQ ID NO:2, wherein the plant is potato, broad bean, beet, spinach, pea, wheat, maize or rice. However, SEQ ID NO:2 is a specific insertion into an Arabidopsis starch phosphorylase gene. Therefore, to meet the limitations of the claim either the exact same insertion would have to be made in Arabidopsis, or the plants mentioned above would have to be transformed with SEQ ID NO:2.

T-DNA insertion mutations can not be targeted

While the specification does disclose an Arabidopsis line DDS72, with a tDNA insert comprising SEQ ID NO:2, in which the starch grain size and/or starch content is altered, it is not demonstrated from the specification that it is the insertion of tDNA in starch phosphorylation that is responsible for this phenotype, and therefore such insertional mutagenesis could be repeated in which such a phenotype would not result from this insertion even if the insertion could be duplicated. However, the insertion of line DDS72 could not be predictably

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repeated in another plant with any reasonable expectation of success, because the insertion was performed using random T-DNA insertion mutagenesis.

As discussed above, insertional mutagenesis is unpredictable. In a review of tDNA insertional mutagenesis, An et al (2005 Plant Cell Physiology 46:14-22) disclose that "The phenotypic alterations observed in a T-DNA –tagged line are not necessarily due to the insertional mutation caused by the element. This is because T-DNA often inserts into more than one locus in a particular chromosome. Alternatively, other elements, such as endogenous transposons, might be involved in the mutant phenotype" (see last paragraph on page 19 for example). An et al also disclose "Therefore it is necessary to confirm those observations by analyzing additional lines that contain a mutation in the target gene" (see last paragraph on page 19, for example).

However, the specification does not give guidance for either complementation studies or analyzing other lines that contain a mutation in starch phosphylase to demonstrate that the insert is responsible for the phenotype. With complementation studies one could show that the alteration of the gene in question actually is responsible for the phenotype rather than another insertion elsewhere in the genome. Without such guidance it would be unpredictable to perform random insertional mutagenesis that arrives at the claimed phenotype. The specification also did not show an analysis of transcript, or even whether or not a protein was made in the Arabidopsis line comprising SEQ ID NO:2. Without demonstrating the mechanism, or that the insert itself is

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responsible for the phenotype, Applicants have not enabled a plant comprising SEQ ID NO:2 with the claimed phenotype.

Even if the claimed insert is responsible for the phenotype, it is unlikely that one would be able to duplicate or practice the invention. As the claimed insertion appears to be a random, one-time event, and is not a targeted insertion, one of skill in the art would not be able to practice the invention without at least having the line DDS72. The claims are not limited to line DDS72, however, and there also does not appear to be a deposit of line DDS72, which would be required for enablement even if the claims are limited to line DDS72.

Species other than Arabidopsis comprising SEQ ID NO:2 would not necessarily result in the claimed phenotype

The claim limitations require the plant to comprise SEQ ID NO:2, and yet, SEQ ID NO:2 is the sequence of an Arabidopsis starch phosphorylase with a tDNA insertion. The claims encompass potato, broad bean, beet, spinach, pea, wheat, maize or rice with the claimed sequence. Either the plant would be required to have an Arabidopsis starch phosphorylase in its genome and then perform insertional mutagenesis, or the plant would simply be transformed with SEQ ID NO:2. The specification does not give guidance for either set of circumstances, and particularly does not give guidance in how either set of experiments would lead to plants with the claimed phenotype.

Transforming a non-Arabidopsis plant with SEQ ID NO:2, would not necessarily silence the endogenous starch phosphorylase, and would not lead to the claimed phenotype. Likewise, even a non-Arabidopsis plant comprising SEQ

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ID NO:1 and then performing insertional mutagenesis and getting an insert that is identical to the one depicted in SEQ ID NO:2, would merely silence (if indeed the insert is responsible for the silencing of starch phosphorylase activity) the Arabidopsis copy of starch phosphorylase and not the endogenous copy of starch phosphorylase.

Given the state of the art, the disclosure by An et al, and the unpredictability as discussed above, it would be undue experimentation for one of skill in the art to evaluate random insertion of tDNA for its effect on starch content and/or starch grain size of the wide variety of plant species with the guidance provided in the specification.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: There is no positive recitation of a method step in either claim 10 or claim 13. Method claims require that at least one step is recited. The claims are currently written in the passive form and therefore do not recite an actual method step.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-11 and 13-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kossman et al (US Patent 6686514).

The claims are drawn to a method for increasing the size of starch grains and/or starch content of a plant or plant part wherein a starch phosphorylase gene is switched off and the transformed plants, plant cell and seed therefrom. It is noted that the claims of 17-18 recite producing a plant with “a” SEQ ID NO:2. This is most broadly interpreted to mean any 2 nucleotides or more of SEQ ID NO:2, and as such reads on any plant comprising an endogenous starch phosphorylase and is therefore anticipated by Kossman et al.

Kossman et al teach the transformation of maize with a nucleic acid molecule in antisense orientation wherein the expression of starch phosphorylase is reduced (see claims 1-14), and plants, host cells, and plant propagation material which includes seeds (see paragraph 31 under Summary of Invention). Because all of the method steps are anticipated (i.e. switching off a starch phosphorylase) and all the product steps are anticipated, the claim limitations are met by the prior art and thus anticipated. Although neither the increase in starch grain size or starch content is disclosed by Kossman et al,

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should the phenotype be considered enabled, it would also constitute an inherent property unless differences between the method steps and/or product claims can be shown.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 10-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Critchley et al (2001 The Plant Journal 26:89-100) and in view of Kossman et al (US patent 6686514).

The claims are drawn to the above and wherein the switching off is accomplished by inserting nucleotides in an endogenous starch phosphorylase.

Critchley et al teach the disruption of a starch biosynthesis enzyme gene by random T-DNA insertion (see page 90, 2nd column, 2nd paragraph, for example) and the screening of starch phenotypes including starch accumulation and the affect of this mutation on starch phosphorylase (see page 92, 3rd paragraph for example).

Critchley et al do not teach the switching off of starch phosphorylase.

Kossman et al teach the transformation of maize with a nucleic acid molecule in antisense orientation wherein the expression of starch

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phosphorylase is reduced (see claims 1-14), and plants, host cells, and plant propagation material which includes seeds (see paragraph 31 under Summary of Invention).

One of ordinary skill in the art, based on the findings of Critchley et al, would have been motivated to test other T-DNA insertional mutants of other starch enzymes and the effect on starch accumulation in the plant.

Given the state of the art and the disclosures by Critchley et al and Kossman et al, it would have been obvious to one of ordinary skill in the art to modify the method of screening for increased starch accumulation using T-DNA insertional mutagenesis as taught by Critchley et al to study the effect of switching off starch phosphorylase as taught by Kossman et al to screen for increased starch accumulation. One of ordinary skill in the art would have been motivated to do so because starch phosphorylase has been identified as an enzyme that would modify starch content by both Kossman et al and Critchley et al and modified forms of starch are in demand in many industrial applications as discussed by Kossman et al in the background of Invention.

No claims are free of the art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRENT PAGE whose telephone number is (571)272-5914. The examiner can normally be reached on Monday-Friday 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571)-272-0975.

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The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brent T Page

/Anne R. Kubelik/
Primary Examiner, Art Unit 1638